SYNOPSIS

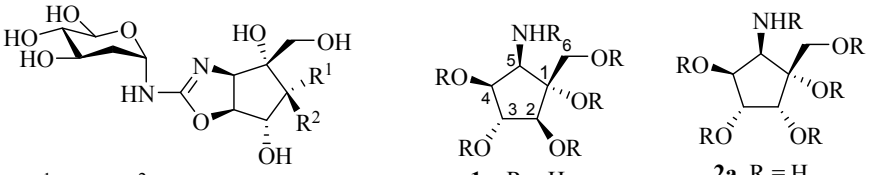
The thesis entitled **"Metathesis based approaches for the synthesis of aminocyclitol moieties of trehazolin and trehalostatin, isoaspinonene, leiocarpin C and (+) goniodiol"** is divided into three chapters.

Chapter I: Stereoselective total synthesis of aminocyclitol moieties of trehazolin and trehalostatin *via* enyne metathesis protocol

This chapter deals with the stereoselective synthesis of aminocyclitol moieties of trehazolin and trehalostatin via enyne metathesis protocol

Trehalose is the characteristic blood sugar and reserve carbohydrate of many insects and trehalase plays an important role in the metabolism of trehalose in insects and fungi.[1] In this way specific inhibitors of trehalase may find applications in the regulating the trehalose metabolism and thus pave way for the discovery of new insecticides. A diverse collection of naturally occurring trehalase inhibitors is known, most often many of which contain an aminocyclopentitol unit. Trehazolin and trehalostatin (Figure1) come under this collection. Therefore, it is not surprising that their total synthesis[2] and the elucidation of SARs[3] have received much interest. Trehazolin, isolated by Ando and coworkers from the culture broth of *Micromono-*

Figure 1



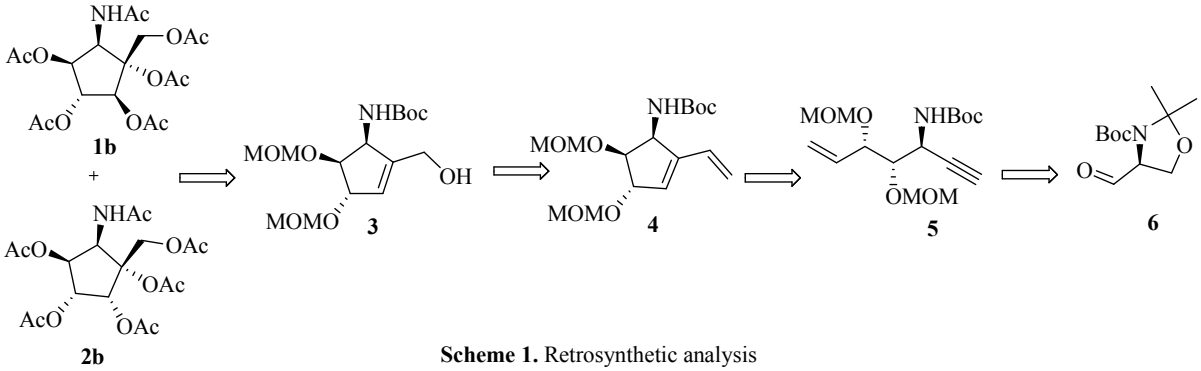
R^1 = OH, R^2 = H; trehalostatin (**1**)
R^1 = H, R^2 = OH; trehazolin (**2**)

1a. R = H
1b. R = OAc

2a. R = H
2b. R = OAc

-spora strain SANK 62390, has been shown to be powerful inhibitor of trehalase *in vitro* (IC_{50} 0.016 μg/mL for silkworm trehalase).[4] Aminocyclopentitol moiety **1a** of trehazolin is known as trehazolamine. Trehalostatin was isolated by Murao *et al.* from the culture broth of *Amycolatopsis trehalostatica*.[5] Interestingly, both the aminocyclopentitols of trehazolin (trehazolamine **1a**) and trehalostatin (*epi*-trehazolamine **2a**) share C-2 epimeric relationship with each other. Structurally, both **1a** and **2a** are densely functionalized with contiguous chiral groups; while the C1 carbon bears a chiral tertiary hydroxy group and a hydroxy

methyl group, the C2, C3 and C4 carbon atoms are endowed with the hydroxy groups and the C5 is decorated with an amino functionality. Due to the above cited reasons, these two aminocyclopentitols are attractive synthetic targets.[2] Herein this chapter the synthesis of both trehazolamine and *epi*-trehazolamine as their derivatives by enyne metathesis protocol is described.



Scheme 1. Retrosynthetic analysis

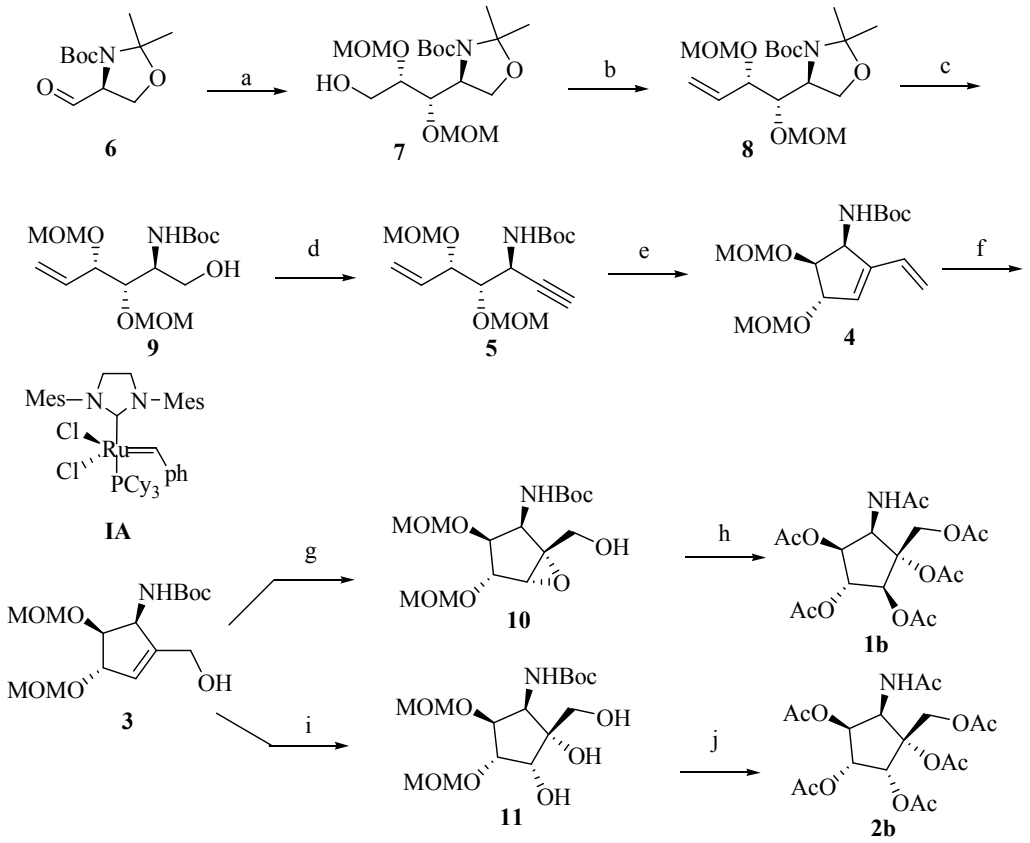
Enyne metathesis[6,7] has emerged as a powerful tool for the construction of carbocylic ring systems. In continuation of the interest on the total synthesis of bioactive aminocyclitols containing natural products,[7] the total synthesis of trehazolamine and *epi*-trehazolamine as their hexaacetates is described. The retrosynthetic analysis of our approach is shown in Scheme 1. Thus the targets **1b** and **2b** could be readily assembled by elaboration of precursor **3** using Sharpless asymmetric epoxidation followed by the regioselective epoxide ring-opening reaction with sodium acetate followed by acetylation. The later could be obtained by the substrate directed dihydroxylation reaction and acetylation. Allylic alcohol **3** in turn was envisioned from 1-vinyl cyclopentene **4** wherein it was presumed that the vinylic double bond would serve as the masked 'hydroxymethyl side chain' that could be generated by a sequential regioselective dihydroxylation-oxidative cleavage-reduction reaction set. While diene **4** was accessed from the enyne **5** *via* the crucial enyne metathesis reaction and the enyne system **5** was realized from Garner's aldehyde **6**.

Results and discussion

Thus, the known precursor[7] **7** (Scheme 2) on Swern oxidation (DMSO/$(COCl)_2$/CH_2Cl_2/Et_3N/-78 ^oC/1 h) and Wittig olefination ($Ph_3P^+CH_3I^-$/KO^{t}Bu/THF/0 ^oC to rt/3 h) furnished olefin **8** (65%). Next the olefin **8** on acetonide deprotection ($CuCl_2.2H_2O$/CH_3CN/0 ^oC/10 min) afforded primary alcohol **9** (95%). Alcohol **9** was oxidized to aldehyde under Swern

conditions and the aldehyde thus obtained was converted into vinyl dibromide (CBr_4/TPP/Et_3N/CH_2Cl_2/-10 ^oC/2 h) which under Grignard conditions (EtMgBr/THF/0 ^oC/10 min) was transformed into a acetylenic compound enyne **5** (88% over three steps). Enyne **5** underwent a facile metathesis reaction {G-II (**IA**, 10 mol%)/toluene/110 ^oC/10 h} to afford the 1-vinylcyclopentene system **4** (91%). Compound **4** was identified from its spectral data. The ^1H NMR spectrum of **4** indicated the absence of acetylenic proton whilst displaying the

Scheme 2



Reagents and conditions: (a) Ref. 7; (b) i) DMSO, $(COCl)_2$, CH_2Cl_2, Et_3N, -78 ^oC, 1 h; ii) $Ph_3P^+CH_3I^-$, KO^{t}Bu, THF, -10 ^oC to rt, 3 h, 65% (over two steps); (c) $CuCl_2.2H_2O$, CH_3CN, 0 ^oC, 10 min, 95%; (d) i) DMSO, $(COCl)_2$, CH_2Cl_2, Et_3N, -78 ^oC, 1 h; ii) CBr_4, TPP, Et_3N, CH_2Cl_2, 0 ^oC, 2 h; iii) EtMgBr, THF, 0 ^oC, 10 min, 88% (over three steps); (e) G-II (**IA**, 10 mol%), toulene, 110 ^oC, 10 h, 91%; (f) i) OsO_4, NMO, acetone: H_2O (4:1), rt, 2 h; ii) $NaIO_4$, MeOH: H_2O (9:1), 5 min, rt; iii) $NaBH_4$, MeOH, 0 ^oC, 5 min, 73% (over three steps); (g) (-)-DIPT, Ti(O^{i}Pr)$_4$, TBHP, CH_2Cl_2, -20 ^oC, 24 h, 60%; (h) i) NaOAc, H_2O: DMF (1:1), 120 ^oC, 24 h; ii) TFA, CH_2Cl_2, 0 ^oC, 8 h; iii) Ac_2O, Py, DMAP, 24 h, rt, 70% (over three steps); (i) OsO_4, NMO, acetone : H_2O (4:1), 4 h, 80%; (j) i) TFA, CH_2Cl_2, 0 ^oC, 8 h; ii) Ac_2O, Py, DMAP, rt, 24 h, 75% (over two steps).

characteristic olefinic protons at δ 6.30 ppm as a double doublet (J = 17.5, 11.7 Hz), at δ 5.76 ppm as a singlet, at δ 5.49 ppm as a doublet (J = 17.5 Hz) and at δ 5.22 ppm as a doublet (J =

10.9 Hz). The HRMS spectrum displayed the $[M+Na]^+$ 352.1727, calculated 352.1736 for the molecular formula $C_{16}H_{27}NO_6Na$.

According to the envisaged plan, the next task was to differentiate between the two olefins and functionalize selectively the vinylic olefin into the hydroxymethyl side chain. Hence, a sequential dihydroxylation-oxidative cleavage-reduction protocol was invoked. Thus, the terminal olefinic bond of the conjugated diene **4** on regioselective dihydroxylation {OsO_4/NMO/acetone:H_2O (4:1)/rt/2 h} furnished the corresponding diol which on oxidative cleavage ($NaIO_4$/MeOH/H_2O/rt/5 min) and reduction of the *in situ* generated aldehyde ($NaBH_4$/MeOH/rt/5 min) gave the crucial allylic alcohol **3** (73% over three steps). Allylic alcohol **3** underwent Sharpless epoxidation[8] {(-)-DIPT/Ti(O^iPr)$_4$/TBHP/-20 ^oC/24 h} to give chiral epoxide **10** (60%) which on ring-opening reaction with the acetate ion {NaOAc/DMF:H_2O(1:1)/120 ^oC/24 h}, one-pot deprotection (TFA/CH_2Cl_2/0 ^oC/8 h) of MOM and Boc groups followed by acetylation (Ac_2O/Py/DMAP/rt/24 h) afforded compound **1b** (70%). Compound **1b** was identical in all respects with the hexaacetate of trehazolamine ($[\alpha]_D^{25}$ +5.9 (*c* 0.4, $CHCl_3$)).[2 h,j]

Likewise allylic alcohol **3** on dihydroxylation[9] (OsO_4/NMO/acetone: H_2O/rt/4 h) gave the corresponding triol **11** (80%) as the major diastereomer (8:2). The requisite major isomer on global deprotection (TFA/CH_2Cl_2/0 ^oC/8 h) followed by acetylation (Ac_2O/Py/DMAP/rt/24 h) afforded hexaacetate of *epi*-trehazolamine **2b** (75%), {$[\alpha]_D^{25}$ -8.5 (*c* 0.4, $CHCl_3$)}. The HRMS spectrum displayed the $[M+Na]^+$ 454.1338, calculated 454.1325 for the molecular formula $C_{18}H_{25}NO_{11}Na$.

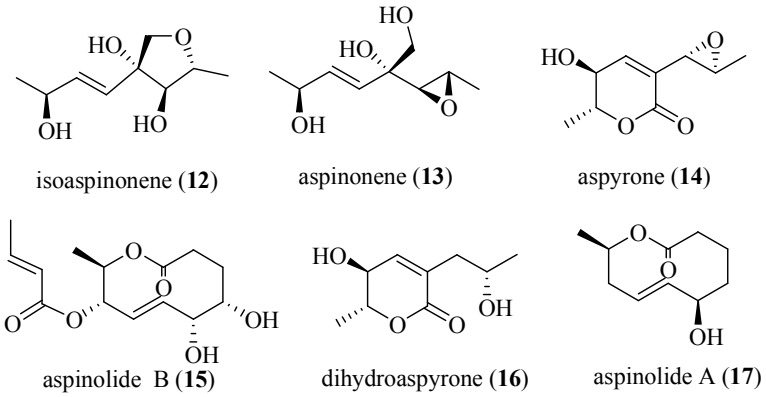
In summary, the stereoselective total synthesis of trehazolamine and *epi*-trehazolamine as their hexaacetates **1b** and **2b** respectively using enyne metathesis as the key step is described herein this chapter. The strategy described could be adopted for the synthesis of similar targets.

Chapter 2: The first stereoselective total synthesis of isoaspinonene *via* Baylis-Hillman reaction and olefin cross-metathesis protocol

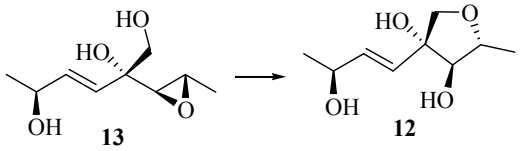
This chapter deals with the first stereoselective total synthesis of isoaspinonene via Baylis-Hillman reaction and olefin cross-metathesis protocol

Isoaspinonene (**12**) was produced from the cultures of *Aspergillus ochraceus.*[10] The other aspinonene/aspyrone co-metabolites are trienediol, aspinolide A, B, C, dihydroaspyrone and dienetriol (Figure 2). All the structures were determined by detailed spectroscopic analysis. Secondary metabolites are useful for transferring their chirality to the desired products.

Figure 2



The tetrahydrofuran **12** considered to be biosynthesized from an intramolecular nucleophilic attack of the primary hydroxyl group on epoxide in co-metabolite **13** (Scheme 3).

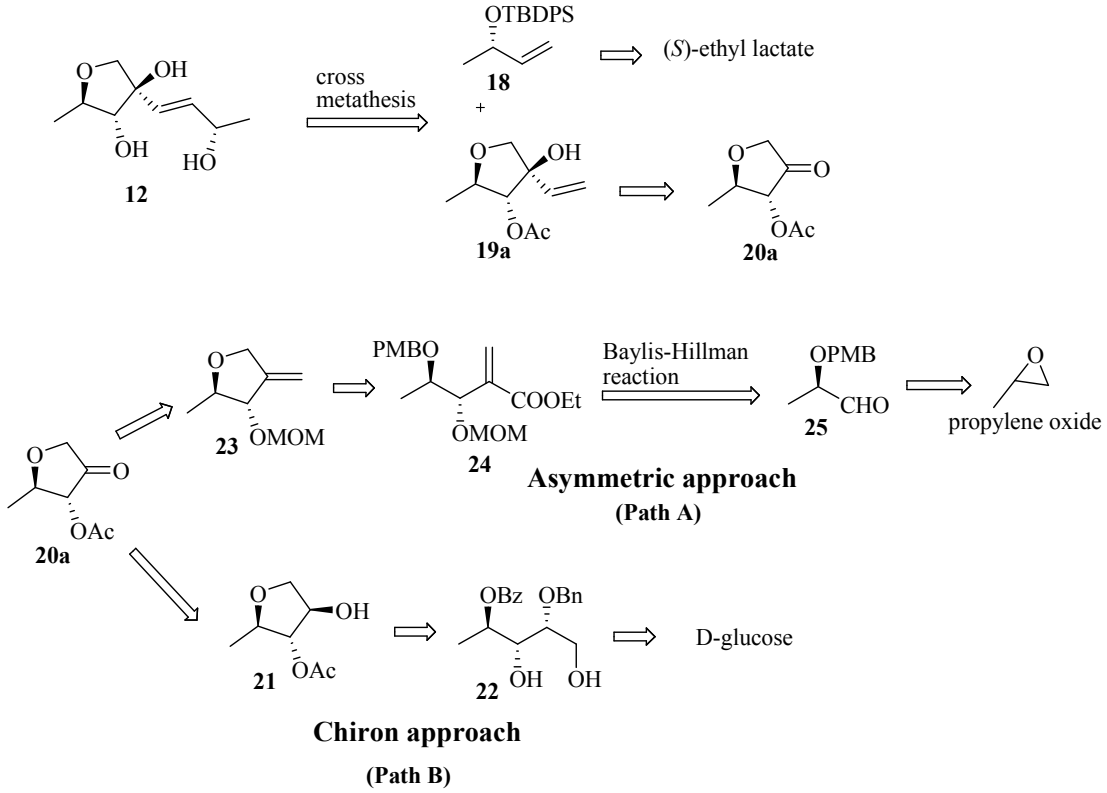


Scheme 3. Proposed biogenetic relationship between **12** and **13**

Tetrahydrofurans are the core unit of many natural products.[11] Construction of optically pure 2,3,4-trisubstituted tetrahydrofuran has remained an attractive target because of its ubiquitous presence as the core structure of furano lignan class of natural products.[12] It was noticed that natural products belonging to this class exhibit '2,3-*trans* and 3,4-*trans*' stereochemistry (e.g., sesaminone, magnolone).[13]

Baylis-Hillman reaction is a well known protocol for the preparation of multifunctional products with a newly created chiral center, predominantly is an *anti*-isomer when the electrophile is a chiral entity. These adducts constitute versatile synthetic intermediates in synthesis of natural products. Over the last few years, our group was involved in expanding the horizon of Baylis-Hillman reaction[14a] and found varied applications of the corresponding adducts.[14b–d] Herein intermediate **24** (Scheme 4) that could be realized from Baylis-Hillman

reaction was identified as an important precursor in the synthesis, which could be used for the synthesis of 2,3,4-trisubstituted tetrahydrofuran **23** which in turn could be used for the total synthesis of isoaspinonene. Baylis-Hillman reaction and tetrahydrofuran ring formation is useful for the synthesis of different 2,3,4-trisubstituted tetrahydrofurans which inturn also useful for the synthesis of other isomers of isoaspinonene.



Scheme 4. Retrosynthetic analysis

As a part of our interest in the stereoselective synthesis of biologically active natural products based on olefin cross-metathesis,[15] a simple and concise route to **12** was devised. Earlier, one of the members from this family, i.e. aspinolide B was synthesized in our group.[16] In continuation, herein, a convergent approach toward the first total synthesis of **12** starting from inexpensive and commercially available starting materials; propylene oxide, D-glucose and (*S*)-ethyl lactate is described.

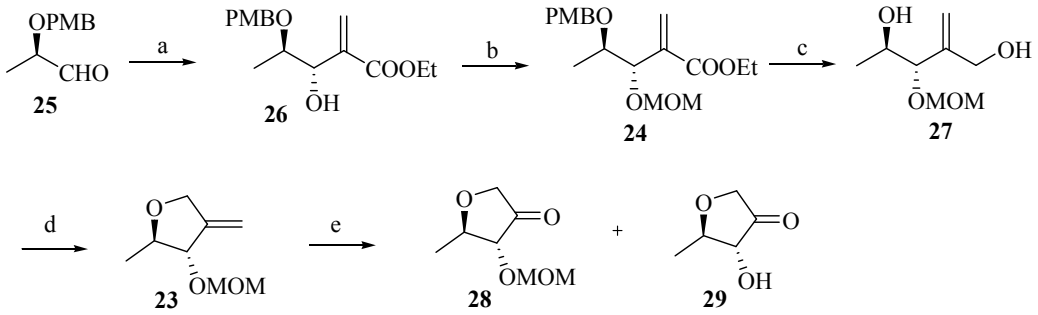
Our synthetic route relies on strategically novel synthetic protocol involving reactions like Baylis-Hillman reaction, Grignard reaction, Wittig olefination, and olefin cross-metathesis. Accordingly, our envisaged retrosynthetic analysis for **12** is based on convergent approach as shown in Scheme 4. *trans*-Olefinic double bond of **12** could be constructed by

the cross-metathesis of olefin **18** with allylic alcohol **19a**. Compound **19a** could be obtained by vinylation of ketone **20a**. For accessing cyclic ketone **20a**, two synthetic routes namely 'asymmetric approach' (Path A) and 'chiron approach' (Path B) are described. Path A could be realized through the MOM-protected cyclic ether **23** which could be obtained from *rac*-propylene oxide using Baylis-Hillman reaction as the key step or by path B from alcohol **21** starting from D-glucose. Alcohol **21** could be obtained from diol **22** and it in turn could be derived from D-glucose. Alternatively, cyclic ether **23** could be prepared from Baylis-Hillman adduct **24**, which could be realised from chiral aldehyde **25** that could be easily generated from propylene oxide. Olefin **18** could be realized from (*S*)-ethyl lactate by TBDPS-etherification, reduction of ester functionality to aldehyde and followed by Wittig olefination.

Results and discussion

As shown in Scheme 5, Baylis-Hillman reaction of aldehyde **25**[16] which could be generated from propylene oxide *via* hydrolytic kinetic resolution, with ethyl acrylate to give adduct **26** (85%) as a mixture of diastereomers (in 9.4:0.6 ratio as determined by HPLC). Secondary hydroxyl group in the adduct **26** was protected using MOM-Cl as its methoxy methyl ether **24** (90%).

Scheme 5

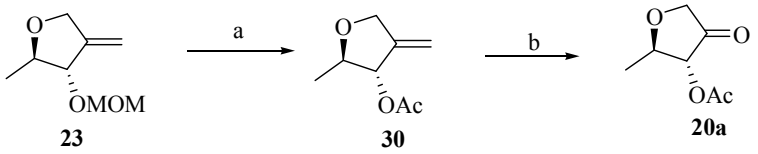


Reagents and conditons: (a) ethyl acrylate, DABCO, DMSO, rt, 24 h, 85%; (b) MOM-Cl, DIPEA, CH_2Cl_2, 0 ^oC to rt, 24 h, 90%; (c) i) DDQ, CH_2Cl_2:H_2O (9:1), 0 ^oC to rt, 1 h, 95%; ii) DIBAL-H, CH_2Cl_2, 0 ^oC to rt, 0.5 h, 93%; (d) TsCl, Et_3N, CH_2Cl_2, 0 ^oC to rt, 24 h, 81%; (e) O_3, CH_2Cl_2, -78 ^oC, 1 h, 95%.

PMB group in **24** was deprotected by treating with DDQ, and the ester group was reduced to alcohol by DIBAL-H to produce diol **27** (88% over two steps). The diol **27** was treated with TsCl for selective tosylation at primary position. Thus, resulted tosyl product on internal nucleophilic substitution by secondary hydroxyl group with concomitant elimination

of the tosyl group led to cyclic ether **23** (81%). Ozonolysis of cyclic ether **23** produced ketone **28** and MOM deprotected ketone **29** (95% combined yield).

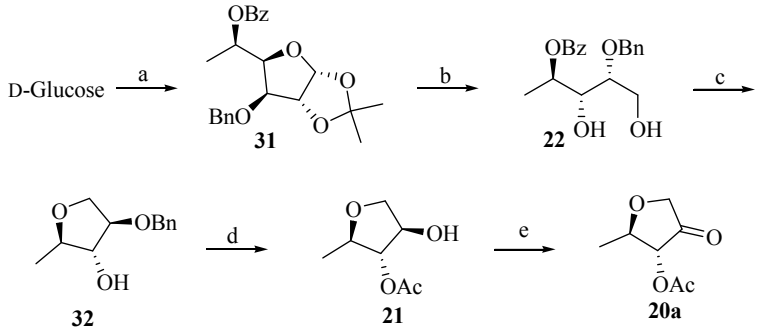
Scheme 6



Reagents and conditions: (a) i) TFA, CH_2Cl_2, 0 ^oC to rt, 1 h; ii) AcCl, Et_3N, CH_2Cl_2, 0 ^oC to rt, 1 h, 90% (over two steps); (b) O_3, CH_2Cl_2, rt, 1 h, 90%.

Under these ozonolysis conditions, it was observed that MOM protecting group was deprotected to result in **29** (15%). Hence, as in Scheme 6, alternate route was contemplated. MOM was deprotected prior to ozonolysis using TFA and the hydroxyl group was reprotected as its acetyl ester **30** (90% over two steps) with AcCl which upon ozonolysis afforded the acetylated ketone **20a** in 90% yield. An acetyl group was considered as the appropriate protecting group because it can survive the ozonolysis conditions.

Scheme 7

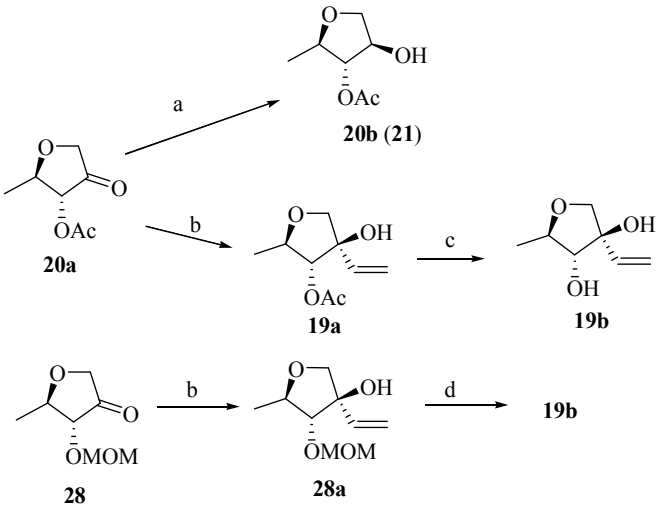


Reagents and conditions: (a) Ref. 17 (b) i) 40% aq. AcOH, H_2SO_4, reflux, 1 h; ii) $NaIO_4$, MeOH:H_2O (9:1), rt, 0.5 h; iii) $NaBH_4$, MeOH, 0 ^oC to rt, 10 min (88% over three steps); (c) i) TsCl, Et_3N, CH_2Cl_2, 0 ^oC to rt, 24 h; ii) K_2CO_3, MeOH, rt, 0.5 h, 81% (over two steps); (d) i) AcCl, Et_3N, CH_2Cl_2, 0 ^oC to rt, 0.5 h, 85%; ii) Pd-C, H_2, EtOAc, rt, 3 h, 90%; (e) DMP, CH_2Cl_2, 0 ^oC to rt, 1 h, 92%.

Chiron approach for the synthesis of **20a** is shown in Scheme 7. Thus the the acetonide group of benzoate ester **31**[17] was hydrolyzed with 40% aq. acetic acid under reflux conditions to furnish the corresponding diol, which on oxidative cleavage using $NaIO_4$ and reduction of the *in situ* generated aldehyde with $NaBH_4$ gave the crucial diol **22** (88% over three steps**)**. The diol **22** on selective tosylation by treating with TsCl resulted in tosylated product, which on intramolecular nucleophilic attack with oxyanion generated using K_2CO_3

produced cyclic ether **32** (81% over two steps). Secondary alcohol of ether **32** was protected with AcCl as acetyl ester (85% yield) and benzyl group of resulted acetyl ester was deprotected under hydrogenation conditions resulted secondary alcohol **21** (90%). Alcohol **21** underwent oxidation by Dess-Martin Periodinane (DMP) resulted in ketone **20a** (92%)**.**

Scheme 8



(a) $NaBH_4$, MeOH, 0 ^oC, 15 min, 95%; (b) vinylMgBr, THF, -78 ^oC, 1 h, 93 and 90%; (c) K_2CO_3, MeOH, rt, 0.5 h,, 90%; (d) TFA, CH_2Cl_2, 0 ^oC to rt, 1 h, 85%.

The ketone **20a** underwent vinylation (Scheme 8) with vinylMgBr to yield crucial tertiary allylic alcohol **19a** (93%) in a diastereomeric ratio of 9:1 (as determined by ^1H NMR spectral analysis) in favor of the required isomer. Herein, unlike the conventional cyclic alkoxy ketones,[18] the present substrate **20a** is endowed with more nucleophilic ring oxygen which participates in the five-membered chelation complex involving ketone functional group with magnesium to facilitate the *anti*-addition to result in compound **19a** in high selectivity.

Table 1. Examples for stereoselective additions to ketones

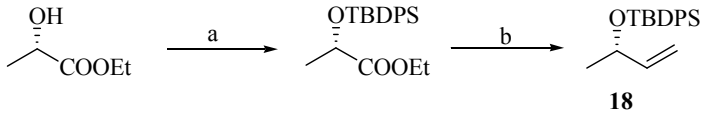
no.	ketone	reagent	solvent	yield (%)	$T(^oC)/t$ (h)	diastereomeric ratio
1	**20a**	vinyl MgBr	THF	93	-78/1	9:1[a]
2	**20a**	$NaBH_4$	MeOH	95	0/0.25	9.1:0.9[b]
3	**28**	vinyl MgBr	THF	90	-78/1	9.5:0.5[a]

[a] Determined by ^{1}HNMR.
[b] Determined by HPLC.

In order to validate the hypothesis that ring-oxygen atom is involved in the complexation during the addition reaction and dictates the stereochemical outcome and not the oxygen of 3-acetoxy/3-hydroxy group/3-MOM-ether, we conducted additional experiments and the results are listed in Table 1. For instance, when **20a** was subjected to the hydride addition (wherein the counter cation is Na^+) the addition occurred as earlier to afford **20b** (entry 2, Table 1). Next, **28** was selected as the test substrate, wherein the vinyl addition reaction proceeded as in the previous case (**20a**) to afford **28a** in high selectivity. Subsequently in order to prove that the addition reaction favored *anti*-products, **19a** and **28a** were subjected to respective deprotection reactions to afford the respective diols (**19b**) which were then compared. It was found that the diols obtained from **19a** and **28a** shared comparable data. This chemical correlation method proves the *anti*-addition of two variable substrates. Interestingly **20b** was identified as the starting material **21** and bear the identical data. Thus these set of reactions established the fact that the ring-oxygen plays the crucial role and not otherwise nor the counter cation has any role in the addition reaction. It also proves the relative *anti*-stereochemistry of C3 and C4 carbons of the addition products unequivocally.

Thus the absolute stereochemistry at C4 was assigned as '*R*' from the above experiments. Allylic alcohol **19a** constitutes an important fragment of the cross-metathesis reaction.

Scheme 9



18

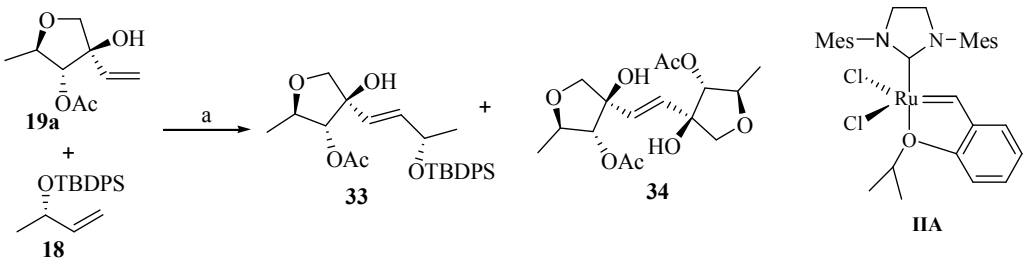
Reagents and conditions: (a) TBDPSCl, imidazole, CH_2Cl_2, 0 °C to rt, 3 h, 96%; (b) i) DIBAL-H, CH_2Cl_2, -78 °C, 1 h; ii) $Ph_3P^+CH_3I^-$, KO^{t}Bu, THF, -10 °C to rt, 6 h, 61% (over two steps).

Next the synthesis of other olefinic partner **18** (Scheme 9) was planned. Thus, TBDPS protected (*S*)-ethyl lactate is underwent reduction with DIBAL-H at -78 °C to give aldehyde, which on Wittig olefination gave olefin **18** (61% over two steps).

In order to construct the main skeleton of the target **12**, coupling of the two olefinic partners **18** and **19a** using olefin cross-metathesis protocol was used. Initially, the reaction in CH_2Cl_2 and toluene as the solvents was attempted. However, the best result was obtained when olefin cross-metathesis was performed using **18** and **19a** in 2:1 ratio, in toluene and at

110 ^{o}C (Table 2, entry 4). All the results are presented in Table 2. As outlined in Scheme 10, the crucial olefin cross-metathesis reaction using Hoveyda-Grubbs II[19] catalyst (**IIA**, 10 mol%/toluene) in between **18** and **19a** (2:1 ratio) resulted in the cross product **33** (60%) as a single stereoisomer with *E*-configuration (as characterized by ^{1}H NMR) in which the olefinic protons resonated at δ 5.82 ppm, J = 15.2 Hz and at δ 5.47 ppm, J = 15.6 Hz indicating the *trans* geometry of olefinic protons and a small amount of homo-dimer **34** (5%).

Scheme 10



Reagents and conditions: (a) Hoveyda-Grubbs-II (**IIA**) 10 mol%, toluene, 110 ^{o}C, 1 h, 60%.

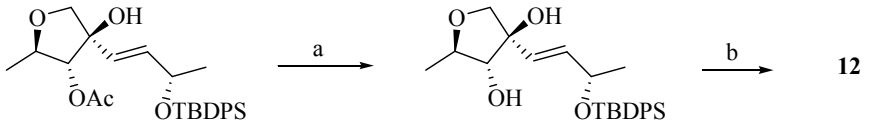
Table 2. Study of the olefin cross-metathesis reaction of **18** and **19a** under various conditions.

Entry	**18 : 19a** (equiv)	Catalyst (10 mol%)	Solvent	Temp ^{o}C	Time	Yield[a] % **33** : **34**
1	1:2	**IIA**	CH_2Cl_2	40	20 h	60 : 10
2	1:2	**IIA**	Toluene	110	1 h	60 : 10
3	2:1	**IIA**	CH_2Cl_2	40	20 h	60 : 5
4	2:1	**IIA**	Toluene	110	1 h	60 : 5

[a] Isolated yields after purification by column chromatography.

Now, all that remained to complete the synthesis was to hydrolyze acetyl ester and deprotect the TBDPS group (Scheme 11). Thus, the cross-product **33** has hydrolyzed in presence of K_2CO_3 to produce **35** (94%) followed by the deprotection of silyl ether with TBAF to furnish the target **12** (80%).

Scheme 11



33 **35**

Reagents and conditions: (a) K_2CO_3, MeOH, rt, 0.5 h, 94%; (b) TBAF, CH_2Cl_2, 0 ^oC to rt, 12 h, 80%.

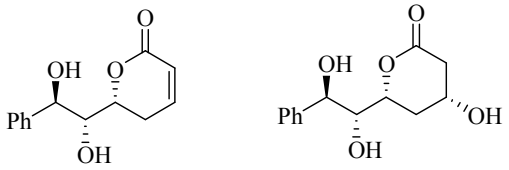
In summary, this chapter describes the first stereoselective synthesis of isoaspinonene (**12**) was achieved by Baylis-Hillman reaction and cross-metathesis strategy which was used to access the advanced intermediate (**33**) that was endowed with all stereogenic centers and was easily transformed to the target compound **12**.

Chapter III: Total synthesis of leiocarpin C and (+)-goniodiol *via* olefin cross-metathesis protocol

This chapter deals with the total synthesis of leiocarpin C and (+)-goniodiol via olefin cross-metathesis protocol

Leiocarpin C (**37**) is a natural styryl lactone. Styryl lactones are natural products exhibiting significant biological activities like antitumor, antifungal and antibiotic properties.[20] Lactone **37** (Figure 3) was isolated from the stem bark of tropical plant *Goniothalamus leiocarpus*.[21] Recently two syntheses of **37** were reported.[22] (+)-Goniodiol (**36**) was isolated from the stem bark of *Goniothalamus gigantus* and from the leaves and twigs of *Goniothalamus sesquipedalis*.[23b] **36** is selectively cytotoxic against human lung carcinoma cells A-549 (ED_{50} = 0.12 $\mu g/mL^{-1}$) and p-388 murine leukemia cells (IC_{50} = 4.56 $\mu g/mL^{-1}$).[23] It is pertinent to mention that there are many syntheses of **36** are reported.[22,24] Impressed with the bio-profile coupled with the group's interest in the synthesis of such pyrone containing natural products,[25] total synthesis of **36** and **37** was undertaken. Herein the total synthesis of **37** and **36** by strategically novel synthetic methodology involving olefin cross-metathesis and dihydroxylation as the key steps to access the basic premise of the skeleton and thence its elaboration to the targets is described in this chapter.

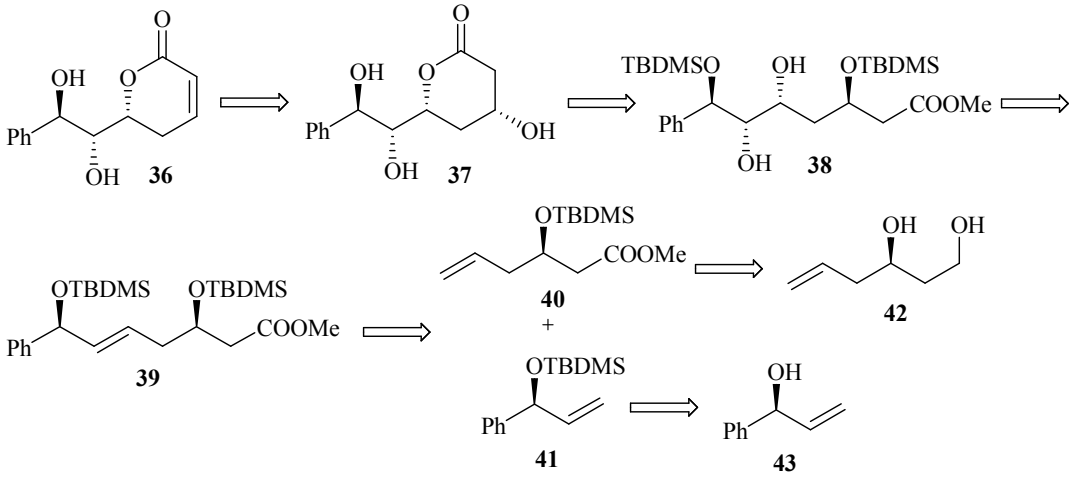
Figure 3



(+) goniodiol (**36**) leiocarpin C (**37**)

The retrosynthetic analysis of our approach is shown in Scheme 12. **36** could be produced from **37** by using a reported procedure.[22b] **37** in turn could be obtained by desilylation/concomitant lactonisation of acyclic skeleton **38**. Compound **38** in turn was prepared by the substrate controlled dihydroxylation of the cross-metathesis product **39**. Olefin **39** could be realized from the cross-metathesis reaction of two olefinic fragments **40** and **41**. While, fragment **40** could be prepared from the known compound **42**[26a] by secondary

Scheme 12. Retrosynthetic analysis



alcohol protection, oxidation of primary alcohol and esterification of corresponding acid as the key steps, the other fragment **41** could be prepared by the TBDMS- etherification of the known phenyl vinyl carbinol (*S*) - **43** that was earlier prepared by us.[26b]

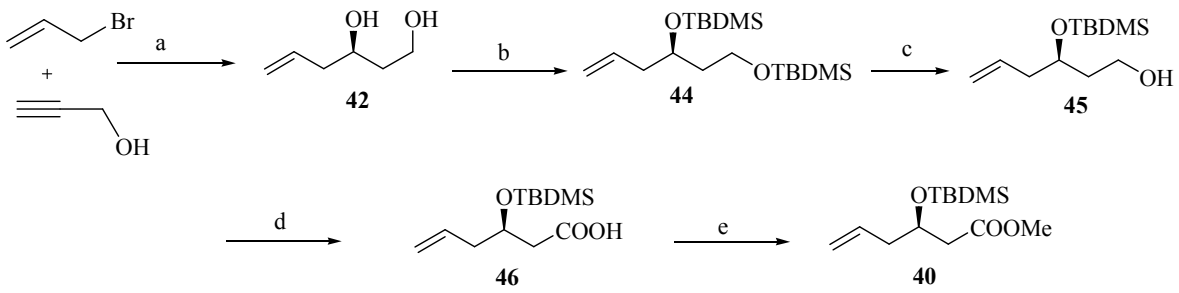
Results and discussion

The synthesis of leiocarpin C commenced by accessing the two fragments **40** and **41** independently.

Synthesis of fragment 40

Accordingly, first olefinic ester **40** was synthesized (Scheme 13). Thus, the secondary alcohol of the known diol **42** was protected as its silyl ether. In order to differentiate between the primary and secondary alcohols, a selective deprotection of the *bis*-TBDMS in the primary position was employed. Thus the *bis*-TBDMS ether **44** was formed (TBDMSCl, imidazole/CH_2Cl_2/0 ^oC/2 h) first followed by the selective removal (PTSA/MeOH/-10 ^oC/30 min) of primary silyl group afforded **45** (74%). Primary alcohol **45** was oxidized to the corresponding aldehyde under Swern oxidation conditions (DMSO/$(COCl)_2$/CH_2Cl_2/Et_3N/-78 ^oC/1 h) which was further oxidized[27] ($NaClO_2$/NaH_2PO_4. $2H_2O$/2-methyl-2-butene/H_2O/0 ^oC/3 h) to the acid **46** (86% over two steps). The resulting acid **46** was subsequently esterified to afford **40** (85%) using diazomethane in ether.

Scheme 13

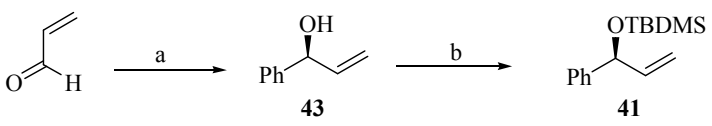


Reagents and conditions: (a) Ref 25a; (b) TBDMSCl, imidazole, CH_2Cl_2, 0 ^oC, 2 h, 95%; (c) PTSA, MeOH, -10 ^oC, 30 min, 74%; (d) i) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2, -78 ^oC, 1 h; ii) $NaClO_2$, NaH_2PO_4, 2-methyl-2-butene, H_2O, 0 ^oC, 3 h, 86%, (over two steps); (e) CH_2N_2, ether, 0 ^oC, 5 min, 85%.

Synthesis of fragment 17

The known phenyl vinyl carbinol **43** was protected (Scheme 14) as its silyl ether **41** (TBDMSCl/imidazole/CH_2Cl_2/rt/80%). Based on our earlier results protection[26b] was warranted for a facile cross-metathesis reaction.

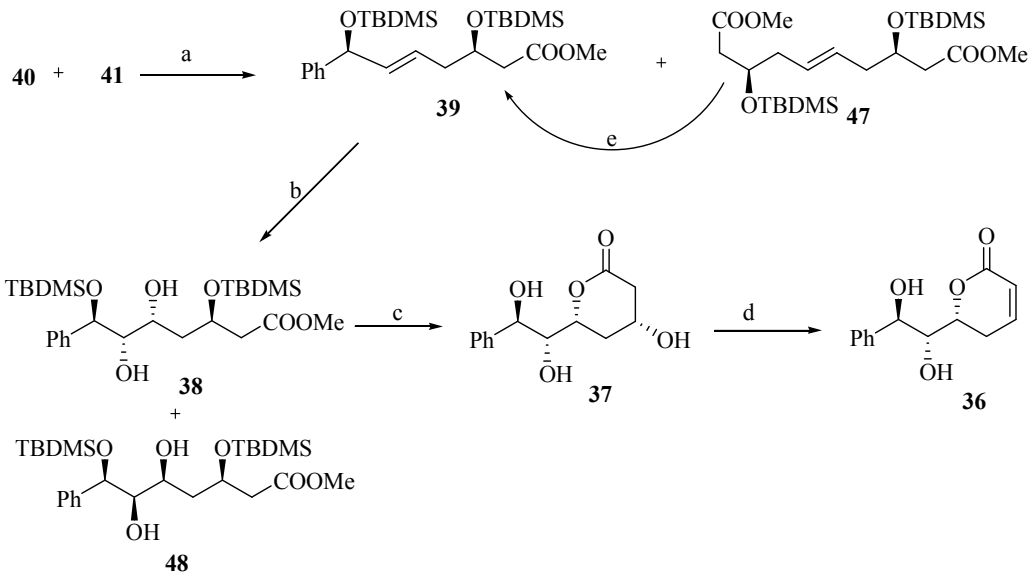
Scheme 14



Reagents and conditions: (a) Ref 25b; (b) TBDMSCl, imidazole, CH_2Cl_2, 0 ^oC, 30 min., 80%.

As outlined in Scheme 15, the crucial olefin cross-metathesis reaction[15,28] using Grubbs'-II (**IA**, 10 mol%/CH_2Cl_2/rt/24 h) between olefinic ester **40** and **41** (1:1.5 ratio) resulted in the cross product **39** (60%) as a single stereo isomer and homo-dimer **47** (5%) of ester olefin **40**. Homodimer **47** was effectively converted to the desired olefin **39** (60%) by using a second cross-metathesis reaction under the same conditions. Subsequently, the cross product **39** was dihydroxylated[29] (OsO_4/NMO/acetone/H_2O in ratio of 4:1/rt) to produce the desired diol **38** as the required major isomer (75%), in a ratio of 80:20 which was separated by column chromatography (minor diastereomer **48** yield is 18%). Diol **38** was treated with amberlyst 15 resin in CH_3CN to furnish the **37** (93%). The physical and spectroscopic data of **37** were identical to the reported natural leiocarpin C $[\alpha]_D^{25}$ -63.1 (*c* 0.30, $CHCl_3$).[21, 22] Compound **37** was converted to (+)-goniodiol (**36**) by the known procedure. Similarly, the spectral data of **36** matched with that of the reported values.[22]

Scheme 15



Reagents and conditions: (a) Grubbs-II (**IA**, 10 mol%), CH_2Cl_2, rt, 24 h, 60%; (b) OsO_4, NMO, acetone:H_2O (4:1), rt, 24 h, 75%; (c) Amberlyst 15, CH_3CN, rt, 2 h, 93%; (d) 21 b; (e) Grubbs-II (**IA**, 10 mol%), **41**, CH_2Cl_2, rt, 24 h, 60%.

In summary, the stereoselective synthesis of leiocarpin C was achieved by cross-metathesis/dihydroxylation strategy to access the advanced intermediate (**38**) that was endowed with all stereogenic centers and functionalities and was easily elaborated to the target compound **37** in total 10 steps and in 24.5% overall yield. Alongside synthesis of (+)-goniodiol **36** was also accomplished.

REFERENCES

1. Elbein, A. D. *Adv. Carbohydr. Chem. Biochem*. **1974**, *30*, 227.
2. a) Ogawa, S.; Uchida, C. *J. Chem. Soc., Perkin Trans. 1* **1992**, 1939. b) Ogawa, S.; Uchida, C. *Chem. Lett.* **1993**, 173. c) Uchida, C.; Yamagishi, T.; Ogawa, S. *J. Chem. Soc., Perkin Trans. 1* **1994**, 589. d) Kobayashi, Y.; Miyazaki, H.; Shiozaki, M. *J. Org. Chem.* **1994**, *59*, 813. e) Ledford, B. E.; Carreira, E. M. *J. Am. Chem. Soc.* **1995**, *117*, 11811. f) Boiron, A.; Zillig, P.; Faber, D.; Giese, B. *J. Org. Chem.* **1998**, *63*, 5877. g) Seepersaud, M.; Al-Abed, Y. *Tetrahedron Lett.* **2001**, *42*, 1471. h) Crimmins, M. T.; Tabet, E. A. *J. Org. Chem.*, **2001**, *66*, 4012. i) Akiyama, M.; Awamura, T.; Kimura, K.; Hosomi, Y.; Kobayashi, A.; Tsuji, K.; Kuboki, A.; Ohira, S. *Tetrhedron lett.* **2004**, *45*, 7133. j) Feng, X.; Duesler, E. N.; Mariano, P. S. *J. Org. Chem.*, **2005**, *70*, 5618.
3. a) Uchida, C.; Ogawa, S. *Carbohydr. Lett.* **1994**, *1*, 77. b) Uchida, C.; Kitahashi, H.; Yamagishi, T.; Iwaisaki, Y.; Ogawa, S. *J. Chem. Soc., Perkin Trans. 1* **1994**, 2775. c) Kobayashi, Y.; Shiozaki, M. *J. Org. Chem.* **1995**, *60*, 2570. d) Uchida, C.; Yamagishi, T.; Kitahashi, H.; Iwaisaki, Y.; Ogawa, S. *Bioorg. Med. Chem.* **1995**, *3*, 1605. e) Uchida, C.; Kitahashi, H.; Watanabe, S.; Ogawa, S. *J. Chem. Soc., Perkin Trans.1* **1995**, 1707. f) Uchida, C.; Ogawa, S. *Bioorg. Med. Chem.* **1996**, *4*, 275.
4. Ando, O.; Satake, H.; Itoi, K.; Sato, A.; Nakajima, M.; Takahashi, S.; Haruyama, H.; Ohkuma, Y.; Kinoshita, T.; Enokita, R. *J. Antibiot.* **1991**, *44*, 1165.
5. a) Murao, S.; Sakai, T.; Gibo, H.; Shin, T.; Nakayama, T.; Komura, H.; Nomoto, K.; Amachi, T. presented at the XV International Carbohydrate Symposium, Yokohama, **1990**. b) Murao, S.; Sakai, T.; Gibo, H.; Nakayama, T.; Shin, T. *Agric. Biol. Chem.* **1991**, *55*, 895.
6. a) Diver, S. T.; Giessert, A. J. *Chem. Rev.* **2004**, *104*, 1317. b) Hu, F.; Zhang, Y.-H.; Yao, Z,-J. *Tetrahedron Lett.* **2007**, *48*, 3511.
7. Radha Krishna, P.; Reddy, P. S. *Synlett* **2009**, 209.
8. Kobayashi, Y.; Miyazaki, H.; Shiozaki, M. *J. Antibiotics* **1994**, *47,* 932.
9. Oh, J. S.; Hong, Y. S.; Kim, Y. G. *J. Ind. Eng. Chem*. **1997**, *3*, 326.
10. Fuchser, J.; Zeeck, A. *Liebigs Ann. Recl.* **1997**, 87.
11. a) Faul, M. M. ; Huff, B. E. *Chem. Rev.* **2000**, *100*, 2407. b) Saleem, M.; Kim, H. J.; Ali, M. S.; Lee, Y. S. *Nat. Prod. Rep.* **2005**, *22*, 696. c) Whiting, D. A. *Nat. Prod. Rep*. **1990**, *7*, 349. d) Whiting, D. A. *Nat. Prod. Rep.* **1985**, *2*, 191. v) Whiting, D. A. *Nat. Prod. Rep.* **1987**, *4*, 499. e) Ward, R. S. *Nat. Prod. Rep.* **1995**, *12*, 183. vii) MacRae, W. D.; Towers,

G. H. N. *Phytochemistry* **1984**, *23*, 1207. f) Ayres, D. C.; Loike, J. D. In Lignans: Chemical, Biological and Clinical Properties; Cambridge University Press: Cambridge, **1990**. g) Kang, E. J.; Lee, E. *Chem. Rev.* **2005**, *105*, 4348.

12. Ward, R. S. *Nat. Prod. Rep.* **1999**, *16*, 75.
13. Chiung, Y. M.; Hayashi, H.; Matsumoto, H.; Otani, T.; Yoshida, K.; Huang, M. Y.; Chen, R. X.; Liu, J. R.; Nakayama, M. *J. Antibiot.* **1994**, *47*, 487.
14. a) Radha Krishna, P.; Sachwani, R.; Reddy, P. S. *Synlett* **2008**, 2897. b) Radha Krishna, P.; Narasingam, M.; Kannan, V. *Tetrahedron Lett.* **2004**, *45*, 4773. c) Radha Krishna, P.; Narsingam, M. *J. Comb. Chem.* **2007**, *9*, 62. d) Radha Krishna, P.; Reddy, P. S. *J. Comb. Chem.* **2008**, *10*, 426.
15. a) i) Radha Krishna, P.; Dayaker, G. *Tetrahedron Lett*. **2007**, *48*, 7279. b) Radha Krishna, P.; Karunakar Reddy, B.; *Tetrahedron Lett.*, **2010**, *51*, 6262.
16. Radha Krishna, P.; Narsingam, M. *Synthesis*, **2007**, 3627.
17. Gurjar, M. K.; Devi, T. R.; Reddy, K. L. N.; Sharma, P. A.; Dhar, T. G. M. *Indian J. Chem. Sect. B* **1993**, *32B*, 995.
18. Maruoka, K.; Oishi, M.; Shiohara, K.; Yamamoto, H.; *Tetrahedron* **1994***, 50,* 8983-8996.
19. a) Garber, S. B.; Kingsbury, J. S.; Gray, B. L.; Hoveyda, A. H.; *J. Am. Chem. Soc.* **2000**, *122*, 8168. b) Radha Krishna, P.; Kadiyala, R. R. *Tetrahedron Lett.* **2010**, *51*, 2586. c) Radha Krishna, P.; Kadiyala, R. R. *Tetrahedron Lett.* **2010**, *51*, 4981.
20. a) Mu, Q.; Tang, W. D.; Liu, R. Y.; Li, C. M.; Lou, L. G.; Sun, H. D.; Hu, C. O. *Planta Med*. **2003**, *69*, 826. b) Pihie, A. H.; Stanslas, J.; Din, L. B. *Anticancer Res*. **1998**, *18*, 1739.
21. a) Mu, Q.; Tang, W.; Li, C.; Lu, Y.; Sun, H.; Zheng, H.; Hoa, X.; Zheng, Q.; Wu, N.; Lou, L.; Xu, B. *Heterocycles* **1999**, *51*, 2969. b) Mu, Q.; Li, C. M.; He, Y. N.; Sun, H. D.; Zheng, H. L.; Lu, Y.; Zheng, Q. T.; Jiang, R. W. *Chin. Chem. Lett*. **1999**, *10*, 135.
22. a) Yadav, J. S.; Krishna, V. H.; Srilatha, A.; Somaiah, R.; Subba Reddy, B. V. *Synthesis*, **2010**, *17*, 3004. b) Yadav, J. S.; Premalatha, K.; Harshavardhan, S. J.; Subba Reddy, B. V. *Tetrahedron Lett*. **2008**, *48*, 6765.
23. a) Collett, L. A.; Davies-Coleman, M. T.; Rivett, D. E. A. *Progress in the Chemistry of Organic Natural Products*. b) In Herz, W.; Folk, H.; Kirby, G. H.; Moore, R. E.; Tamm, C.; Eds.; Springer: Wien, **1997**, *30*, 181. c) Talapatra, S. K.; Basu, D.; Deb, T.; Goswami, S.; Talapatra, B. *Indian J. Chem., Sect. B* **1985**, *24*, 29.
24. a) Prasad, K. R.; Gholap, S. L. *Tetrahedron Lett*. **2007**, *48*, 4679. b) Tate, E. W.; Dixon, D. J.; Ley, S. V. *Org. Biomol. Chem*. **2006**, *4*, 1698. c) Deligny, M.; Carreaux, F.;

Carboni, B. *Synlett* **2005**, 1462. d) Banwell, M. G.; Coster, M. J.; Edwards, A. J.; Karunaratne, O. P.; Smith, J. A.; Welling, L. L.; Willis, A. C. *Aust. J. Chem*. **2003**, *56*, 585. e) Ramachandran, P. V.; Chandra, J. S.; Reddy, M. V. R. *J. Org. Chem.* **2002**, *67*, 7547.

25. a) Radha Krishna, P.; Ramana Reddy, V. V. *Tetrahedron Lett*. **2005**, *46*, 3905. b) Radha Krishna, P.; Srinivas, R. *Tetrahedron: Asymm.* **2007**, *18*, 2197. c) Radha Krishna, P.; Srinivas, R. *Tetrahedron Lett*. **2007**, *48*, 2013.
26. a) Radha Krishna, P.; Krishnarao, L.; Reddy, K. L. N. *Beilstein J. Org. Chem.* **2009**, *5*, No. 14. doi:10.3762/bjoc.5.14. b) Radha Krishna, P.; Shiva Kumar, E. *Tetrahedron Lett*. **2009**, *50*, 6676.
27. Bal, B. S.; Childers Jr. W. E.; Pinnick, H. W. *Tetrahedron* **1981**, *37*, 2091.
28. a) Chatterjee, A. K.; Grubbs, R. H. *Angew. Chem., Int. Ed*. **2002**, *41*, 3171. b) Grubbs, R. H. *Tetrahedron* **2004**, *60*, 7117. c) Nolen, E. G.; Kurish, A. J.; Wong, K. A.; Orlando, M. D. *Tetrahedron Lett*. **2003**, *44*, 2449.
29. Saito, S.; Morikawa, Y.; Moriwake, T. *J. Org. Chem.* **1990**, *55*, 5424.